THE ASSOCIATION OF GALLSTONES AND HEART DISEASE*

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THE ASSOCIATION OF gallstones and heart disease is an old subject, often discussed over the years. I believe that such discussions are of value, and that very practical help for the general surgeon may come out of them. I use the term "gallstones" here rather than "gallbladder disease," for I believe we all agree that the surgery of the *non-calculous* gallbladder is a rather discouraging field of endeavor.

John Hunter, probably the greatest figure in the history of British Surgery, died 160 years ago at a Hospital Board Meeting, during one of his anginal attacks.[10] It is interesting that his friend and physician, Edward Jenner, is said to have predicted during life that Hunter suffered from both gallstones and heart disease, and to have proved at autopsy that he was correct in this clinical impression.[4]

Active interest in the clinical association of gallstones and heart disease, in this country, goes back to Babcock,[1] who in 1909 reported 13 patients in whom he felt that biliary tract disease was adversely affecting their heart ailments. In spite of anesthetic and other problems he was courageous enough to operate on ten of these very ill patients. There were three postoperative deaths. Four of the survivors were thought to have great improvement in their heart disease. In more recent years Gilbert,[8, 9] Ravdin,[19] Hodge,[13, 14] and others,[2, 7, 16, 17, 22, 24, 25, 27] have stimulated a great deal of clinical and experimental work on this general problem, with interesting and important findings. It seems to me that the problem may be divided into three main considerations: (1) the problem of mimicry, leading to mistaken diagnosis; (2) the problem of coexistence, and decision as to the relative role that each factor is playing; and (3) the consideration of evidence as to whether or not gallstone disease may make worse existing coronary disease.

In a recent editorial in *Surgery, Gynecology and Obstetrics*,[5] the following three sentences appear in sequence. "Cardiologists have been impressed by the frequent association of coronary heart disease and gallbladder disease. The differentiation between biliary colic and an attack of angina is at times most difficult. There is a certain amount of evidence that coronary symptoms are aggravated by recurrent attacks of biliary colic." It would be hard to find fault with any of these three statements, but the matter is not as simple as this sounds, and there remain areas of much disagreement among clinicians.

Biliary tract pain is usually referred along the seventh and eighth thoracic spinal segments; heart pain along the fifth to eighth cervical and first to fourth thoracic spinal segments. Yet the pain of biliary colic may not be abdominal at all. The severe pain of biliary colic may simulate cardiac pain closely. It is often substernal rather than abdominal, and may

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actually radiate to the shoulders and down the arms. Blalock[3] analyzed the radiation of pain in a large number of patients with biliary colic. If radiation occurred, it was to the right shoulder in 40 per cent, the right back in 34 per cent, to both shoulders in 8 per cent, and to the left shoulder and left back in 10 per cent. On the other hand cardiac pain may radiate to the abdomen. In either condition a feeling of impending doom and of tight "constriction" of the chest are characteristic. Many patients go along without the benefit of needed surgery due to this mimicry, and a false diagnosis of a disorder of the heart. In such cases failure to diagnose gallstones may be due to failure to even think of this possibility. The most helpful guide toward diagnosis is a good history. Pain that begins without exertion and awakens the patient from sound sleep is far more likely to be of biliary tract origin.

There seems no doubt that, especially in patients over 50, gallstones and heart disease tend to coexist. In a study of some 1200 patients with gallstones, Heuer[12] found a definitely higher incidence of heart disease than is indicated by Life Insurance Companies' figures for the general population. It is hard to know if gallstones, in some way, provoked this, or if patients of this general type are more likely to develop stones. It has been thought that the same type of infection that damaged the gallbladder also damaged the heart,[15] or that some metabolic disturbance led to both gallstones and to fatty changes in the heart and its vessels.[26] Recently attention has been focused more on the possibility that nervous stimuli originating in the gallbladder and common duct may markedly alter coronary blood flow. Gilbert[9] points out that there are "many clinical observations associated with heart disease, which are difficult to explain only on the basis of *intrinsic* anatomical changes in the coronary vessels," and can best be explained by "the assumption of vasomotor changes in the caliber of the coronary vessels, decreasing the flow volume. Such decreases in coronary flow from extrinsic factors may produce the same disproportion between blood supply and blood needs as do anatomical changes in the vessel walls, which restrict the coronary flow when additional demands are made upon it." No less an authority than P. D. White[26] agrees that "a troublesome gallbladder . . . may seriously disturb cardiac function in the presence of otherwise silent coronary disease."

The metabolic factors are difficult to analyze, but there must be some primary disturbance of lipoid-cholesterol metabolism that is at fault in both atherosclerosis and gallstones. Both conditions have a high incidence in diabetes. Another intriguing association that has been described is that of coronary disease and painful shoulders, with supraspinatus calcification. Breyfogle,[6] following a careful statistical study of 1493 necropsy records, concluded that there is "a striking and positive association, regardless of age or sex, between gallbladder disease and coronary artery disease where the latter is regarded as the direct cause of death or the primary contributing factor toward death." White and associates[26] studied 2737 autopsy records at the Massachusetts General Hospital, of patients 20 years old or more. Gallbladder disease was found to be almost twice as common in patients with coronary disease. They felt that "some factor or factors related in part at least to an aging process" were responsible for both conditions. There was no statistical association of peptic ulcer and heart disease. Similar conclusions may be supported by long lists of references gathered by various reporters.[15, 23, 25]

One obvious objection to all this is the general fact that gallstones are more common in women and coronary disease is more common in men. However, the more

severe forms of acute cholecystic disease are rather characteristically found in men. Why this is so I have no idea. Most of Babcock's[1] operative cases were males. The majority of cases of cholecystitis in males occur late in life, while two-thirds of the cases in females occur before the age of 50. When males do have cholecystic disease, it seems to appear late, to be more severe, and more likely to be associated with heart disease.[23]

The main points that stand out, in a forest of statistics, are that gallstones and heart disease frequently coexist, that the symptoms (especially the pain) may be almost identical in the two conditions, and that it is extremely important for the clinician to solve the puzzle correctly. It may prove disastrous to operate on a patient with coronary occlusion under a mistaken impression of upper abdominal surgical disease. It may be almost equally harmful to withhold operation from a patient with gallstones because of the impression of serious coronary disease. A painstaking history and alertness to the problem should lead one toward roentgenologic help and other assistance for correct evaluation.

The third general problem that I mentioned at the outset is that of the actual influence on coronary blood flow of stimuli originating in the upper abdomen. The old clinicians seem to have been well aware of some such factor. Heberden,[11] in 1786, in writing of anginal pain, stated that "those who are afflicted with it are seized while they are walking, and more particularly if they walk soon after eating," and Osler[18] wrote that "of the exciting causes (of angina pectoris), there are three important elements: muscular exertion, mental emotion and digestive disturbances." He also noted that belching gas might coincide with the ending of an anginal attack.

Gilbert[9] has shown that distention of the stomach in dogs caused marked decrease in coronary flow. This did not occur after atropine or vagal section. Similar impressions followed studies of human anginous patients.[8] When breathing 10 per cent oxygen, such patients developed anginal pain much more quickly after meals. This reduced pain-appearance-time was abolished by atropine. Gilbert[9] described an interesting observation of Van Dellen who observed a patient with a paraesophageal hiatus defect whose electrocardiogram was normal when herniation was not present, but presented a "typical coronary curve" when herniation occurred. Many studies, both experimental and clinical,[7, 13, 14, 16, 27] have been made of electrocardiographic changes due to stimuli from the biliary tract. The results have been very variable. In general, the changes in humans *without* coronary disease were insignificant,[14] while those *with* coronary disease showed definite effects from stimuli such as distention of the gallbladder or common duct. The same was true in dogs,[13] the normal dogs showing no significant changes, while in those in which the hearts had been made abnormal (by ligation of small coronary branches or sclerosing injections), changes were produced in the RS-T segments of the electrocardiograms. Great caution must be exercised in interpretation of such experiments. Hodge and Messer[14] found that even routine preoperative medication at times produced electrocardiographic changes. It is no wonder that some apparently significant effects of biliary distention have not been observed by other investigators using similar methods. Ravdin[21] and his associates have recently developed better methods of demonstrating that stimuli from the biliary tract may lessen coronary blood flow. There seems no doubt that this is true.

This leads us to the probability that many patients with heart disease and gallstones would benefit from cholecystectomy. Fortunately, this has been observed with encouraging frequency. Fortunately, too,

with suitable anesthesia such patients stand surgery surprisingly well. A word of caution is needed here to curb too great surgical enthusiasm. We must remember that many patients with gallstones have no evidence whatever of heart disease, that by no means all patients who have both conditions are benefited by gallbladder surgery, and that fatal coronary occlusion may occur during or soon after cholecystectomy, undertaken in the hope of favorably influencing coronary disease. There is still a place for cholecystostomy in an occasional very ill patient. Rest in bed, some weight loss, changes in diet, and other factors incidental to the operation may at times deserve the credit for cardiac improvement that has been awarded to the operation itself.

The general outlook in this field is highly optimistic, nevertheless. It seems clear not only that gallbladder disease may produce harm to the heart, but also that its effects on the heart are reversible, to some extent at least. Many clinical histories are available to support this conclusion. I should like to offer a few brief case histories that have impressed us at Roosevelt Hospital. There is potentially much of "hindsight" in this field and it is difficult to keep it from coloring one's thinking. As Dr. Merrill Sosman of Boston has often pointed out the "retrospectoscope" is a wonderful diagnostic aid. I shall merely present the case reports in brief outline and not attempt to analyze them, beyond offering the opinion that among the 11, the best examples of mimicry are Cases 2 and 7, the best example of simple coexistence is Case 6, and the best example of deleterious effect of gallstones on coronary flow is Case 10.

Case 1. (D. B.) #43366. A 40-year-old physician was admitted to Roosevelt Hospital on June 3, 1952, because of anginal pain. Past history included a bout of infectious hepatitis in the Army eight years previously. The present illness began with occasional precordial pain on exertion, which became marked 3 days before admission, radiating to the left shoulder. The most severe attack occurred while walking up a hill. It subsided in a few minutes, but returned the following day. There was no nausea and no sweating; E.K.G. showed T-wave inversion. He remained in bed in the hospital for 5½ weeks and received anticoagulant therapy. Serial E.K.G.'s showed increasing evidence of myocardial infarction for the first week, then gradual improvement, with a perfectly normal record 4 weeks after onset.

Three months later he was awakened at night by transient pain suggesting biliary colic and later roentgenologic studies revealed gallstones. After some discussion it was decided to postpone operation due to his recent myocardial infarction. The following morning he was awakened by very severe biliary colic, and he did not wish to face the prospect of similar future pain. Cholecystectomy was done without difficulty. There were two calculi in the gallbladder, one 2 cm. in diameter and the other 1 cm. in diameter. The gallbladder was chronically diseased and thickwalled. He left the hospital on the 12th postoperative day and resumed his medical practice rather promptly.

One year has elapsed since operation. There have been twinges of precordial pain, but no definite attacks.

Case 2. (W. B.) #37586. A 66-year-old man (previous partial colectomy for carcinoma of sigmoid—favorable prognosis) was admitted to Roosevelt Hospital for common duct exploration. Four years previously he was said to have a coronary occlusion, and electrocardiograms were said to show a "left heart block." He was hospitalized at that time. After 4 years of freedom he had another attack of severe substernal pain. He was anxious to stay in his hotel apartment, so a hospital type bed was obtained to make it easier to care for him. After 2 weeks, his wife noted slight jaundice, and this led to re-evaluation of the problem. He was then admitted for exploration. Stones were found in the gallbladder and in the common duct. He has done well since (18 months).

Case 3. (M. C.) #16244. Patient was first admitted in August, 1941, at the age of 70, with known hypertension of 10 years' duration, with mild cardiac symptoms. E.K.G. showed ample evidence of myocardial disease.

At 1 A. M., after an unusually strenuous day, she was awakened suddenly by anterior chest pain that radiated down the arms, especially the right arm, down to the fingers. After two or three hours the pain cleared, but it returned 24 hours later and was so severe she "wanted to scream." Diagnosis was myocardial infarction, and she spent 6

weeks in bed. Blood pressure rose gradually from 128/72 to 174/90.

Five years later patient was readmitted with precordial pain. The following day there was pain and tenderness in the right side of the abdomen. The W.B.C. was 17,900 (Polys 89 per cent) and the physical findings suggested acute appendicitis. Under anesthesia, one could easily feel a huge, long gallbladder. It was found to be almost gangrenous, and contained 32 stones. She made an uneventful recovery, and soon resumed her work as a teacher of French.

Six years later (now 81 years old) she was readmitted on account of dyspnea. She had had a fractured hip pinned the previous year and had been doing generally well except for some ankle edema and dyspnea on exertion. There had been no further anginal pain during the years since cholecystectomy. After 8 days in the hospital she was discharged "improved." She died the following year at 82.

Case 4. (P. L.) #63790. A 69-year-old housewife entered Roosevelt Hospital on October 4, 1950, being referred for cholecystectomy by her gynecologist. She had ample evidence of cholelithiasis over a period of at least 5 years, but her physician thought it unwise to consider operation because of hypertensive cardiovascular disease of severe degree. (At the time of admission blood pressure was 230/120.) She had been fairly comfortable, with great dietary restriction, and this had caused marked loss of weight. Cholecystectomy was done under pentothal curare anesthesia. The gallbladder contained 5 dark mulberry stones; recovery was uneventful. She was seen 3 years later, at which time she was eating a full diet, had gained weight to a normal level; she stated that she felt very well. Her hypertension appeared somewhat improved, but no doubt was much the same as before.

Case 5. (G. M.) #81035. A 55-year-old man, admitted to Medical Service at Roosevelt Hospital on August 27, 1953, with history of 3 days of precordial pain, onset following a heavy meal. The pain was substernal but radiated down right arm and to left shoulder and back. The initial pain subsided in a few hours, but he was awakened from sleep that night. After 2 more days of pain he walked 20 blocks to the hospital. Electrocardiograms showed T-wave changes, but reverted to normal in 3 days. Gallbladder Series showed multiple stones. He wished to go home, and was readmitted 2 months later for cholecystectomy, after which he made a normal recovery.

Case 6. (O. P.) #36952. A 58-year-old German construction engineer entered the Roosevelt Hospital on March 21, 1946. He was found to have a myocardial infarction and was very ill. He remained in the hospital 3 months. Six months later he was readmitted due to frequent anginal attacks, brought on by exertion or emotion. He also had attacks suggestive of biliary colic and the patient himself felt that he could distinguish between the two types of pain. He was followed in the Cardiac Clinic for several years. In January, 1951, 5 years after his original admission, cholecystectomy (for stones) was finally done. His convalescence was uneventful except for transient urinary difficulties.

For 2 years after operation he was doing very well. At that time he developed bronchopneumonia and was readmitted with ample evidence of his myocardial disease. After 5 weeks, he was discharged improved. There seems no doubt that he has been generally better since the cholecystectomy. Whether or not this altered his basic myocardial difficulties is very doubtful.

Case 7. (P. R.) #35179. This 67-year-old man entered Roosevelt Hospital on December 6, 1945. There was a 5-year story of anterior chest pain and indigestion, always rather mild in degree. On Labor Day, 1945, after a meal, he had a severe attack of anterior chest pain and felt that "a steam roller" was going across his chest. A physician gave him morphine, called an ambulance and took him to the hospital (in his home town in Connecticut). After ten days he was allowed to go home, being told to give up his job, and to climb no stairs. The latter advice included remodeling his house so that a bathroom and bedroom could be constructed on the ground floor. He also was forbidden to go to his favorite bar, which meant a walk uphill. This advice depressed him greatly.

During the next three months he had many attacks of severe substernal pain, several of them awakening him out of a sound sleep. His daughter, a registered nurse, brought him to the Roosevelt Hospital where roentgenologic studies showed multiple small gallstones. Cholecystectomy did not seem to disturb him in any way and his recovery was smooth.

Eight years have passed since operation. He is now 75 and a very active, vigorous man. He eats heartily and does a lot of work around his home without discomfort.

Case 8. (A. S.) #75584. A 50-year-old manufacturer entered Roosevelt Hospital on September 30, 1952. Past history revealed appendicectomy in 1938, and a history of suspected duodenal ulcer.

For a dozen years he had been having indigestion, and upper abdominal discomfort and gallbladder disease was suspected. Repeated cholecystograms were said to show no stones, but a gallbladder shadow of less than normal density. The problem of roentgenologic interpretation was complicated by obesity. In the fall of 1951, he was taken home from his office in a severe attack with sweating and substernal pain. This soon subsided. In April, 1952, he had another attack, in his office, of severe substernal pain, and was taken home where a physician treated him for a supposed coronary occlusion. He was not satisfied with this diagnosis and some weeks later he went to a well-known Clinic in another city, where he was told that he had no heart disease but did have gallstones. Three months later he had a cholecystectomy at Roosevelt Hospital. The gallbladder was only very slightly diseased. It contained about 50 small stones. No evidence was seen or felt that he had ever had a duodenal ulcer.

One year after operation, he stated that he had been entirely well and free of symptoms. It is likely that this man would have been operated on many years earlier if roentgenologic studies of the gallbladder had shown more definite abnormality. It is interesting that after many years of rather typical gallbladder discomfort, two attacks of a new type appeared that simulated coronary attacks very closely.

Case 9. (O. V.) #14941. A graduate nurse was first admitted to Roosevelt Hospital in May, 1939, at the age of 50, on account of chest pain. She spent 6 days in the hospital. Nothing was found to explain the pain. She was rather "heart-conscious," having had rheumatic fever as a child and having been refused insurance by a leading Insurance Company, while in her twenties, on account of a "heart murmur."

In May, 1942, she was readmitted with severe left anterior chest pain of 8 hours' duration, with radiation down the left arm. She remained in the hospital 41 days with diagnosis of myocardial infarction.

There were subsequent similar attacks, and in June, 1945, she was admitted to the hospital for the seventh time, with severe pain along the left sternal margin of 2½ hours' duration. "Heavy pressure" and "burning" were her descriptive terms. She had been awakened from sleep on this occasion. Nitroglycerine seemed to lessen the discomfort.

At the time of her ninth hospital admission in November, 1946, a thickwalled gallbladder containing a large single stone was removed. She then took an easy nursing job in a college infirmary, but became bored and returned to special duty bedside nursing. She is moderately hypertensive, as she has been for many years, but is entirely symptom free. She works hard and regularly, at the age of 64, 7 years after the cholecystectomy.

Case 10. (L. P. W.) #18711. Patient was first admitted to Roosevelt Hospital in January, 1943, at the age of 70. The diagnoses were diabetes and hypertension. Six years later she was readmitted with the same diagnoses plus a urinary infection which necessitated right nephrectomy.

In December, 1949, she was readmitted for evaluation of hypertensive arteriosclerotic heart disease, coronary sclerosis, and angina pectoris. She had been having severe and frequent anginal pain on exertion or emotion, relieved by nitroglycerine. A new item appeared, namely right upper quadrant pain. This was found to be due to cholelithiasis. With considerable hesitation surgery was advised, and a mildly diseased gallbladder containing a single stone was removed. Another episode of transient substernal pain occurred 4 months later, but she has done generally well, and during the past summer at the age of 80, she gave an exhibition of her recent water colors. She still has diabetes and hypertensive heart disease, but her son reports that she has been very much more comfortable during the 14 months since she got rid of her gallstone.

Case 11. (B. W.) #61262. Patient was admitted to Roosevelt Hospital at age of 73, complaining of "gallbladder trouble" of 6 years' duration. There had been a lot of digestive trouble and right upper quadrant pain, but only two episodes of severe biliary colic. She was a known hypertensive of 10 years' duration. Several physicians had discussed the matter of cholecystectomy, but had agreed that her heart was "too bad" to stand operation. Blood pressure was 176/100; E.K.G. showed left bundle branch block. Cholecystectomy revealed a rather normal gallbladder containing more than 50 facetted stones. She went home on the 11th postoperative day after a smooth recovery.

Nearly 4 years have elapsed since cholecystectomy. At the age of 77 she is very active and free of complaints, and has recently taken a trip to California.

SUMMARY

The association of gallstones and heart disease, a much-discussed subject, offers three general problems for the surgeon.

First, the problem of mimicry, which may make differential diagnosis difficult. Second, the problem of coexistence, in which the relative role of each condition may be hard to establish; and third, the problem of attempting to benefit coronary disease by elimination of gallstones. With good anesthesia and good surgery, this is a surprisingly safe field of surgical endeavor, and the results justify more frequent resort to it.

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